

### REMARKS

Applicant notes with appreciation the detail and thoroughness embodied in Paper No. 20081110 and the opportunity to distinguish the pending claims over the prior art of record.

Currently, claims 1-7, 9, 10, 13-16, 18, 21, 23, and 26-30 are pending. Claims 8, 11-12, 17, 19-20, 22, 24-25, 31-63 are canceled.

Claims 1 and 26 are currently amended to clarify that an inorganic pyrophosphatase is not present in the portion of the process whereby an amplification product is produced. Applicant submits that as claims 1 and 26 as initially filed recited that the product comprised a quantity of inorganic pyrophosphate, that the claims did not read on the cited prior art of Kwok and Tabor, and the current amendments are not intended to further limit the scope of the pending claims or relinquish any equivalents. These amendments find support in the specification as filed *inter alia* page 11, lines 10-23. As such, no new matter is introduced by way of amendment.

In the Office Action of 20 November 2008 claims 1-7, 9, 10, 13-16, 21, and 26-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523).

Claims 18 and 23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) and further in view of Jack et al. (WO 01/23411 A2).

**Remarks directed to the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523).**

Withdrawal of the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al.

(US Pat. No. 5,498,523) is respectfully requested in light of the current amendments to claims 1 and 26 and as Kwok et al. in view of Tabor et al. fails to teach or suggest all elements in the claims, or provide motivation and a reasonable expectation of success from the combination.

Applicant incorporates by reference the remarks previously made of record regarding the shortcomings of Kwok et al. alone and in view of Tabor.

#### Graham Factual Findings and Response Thereto

Graham factual findings are previously made of record 4 August 2008 and are explicitly repeated in Paper No. 20081110 at pages 4-6.

Applicant incorporates by reference the remarks made of record 4 August 2008 that Kwok et al fails to teach or suggest the claimed steps of: producing a purified reaction product; purifying the nucleic acid synthesis product to obtain a purified reaction product; inactivation of an inorganic pyrophosphatase; and that the steps are performed in a single reaction tube.

#### Resolution of One of Ordinary Skill in the Art

Applicant notes with appreciation the explicit assertion of characteristics related to one of ordinary skill and the art found in Paper No. 20081110 at page 10.

#### Rationale for Obviousness

The Federal Register obviousness examination guidelines detail seven possible rationales for a finding of obviousness. These rationales are reproduced below.

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) “Obvious to try”—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

(Federal Register, Vol. 72, No. 195, 57529).

The basis of the rejection remains that “[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Tabor to the method taught by Kwok.” (Paper No. 20081110, page 6.) Motivation for combining the “PCR and primer extension steps” of Kwok et al. with the inorganic pyrophosphatase of Tabor et al. is provided by the teaching of Tabor et al. “that inorganic pyrophosphatase degrades inorganic pyrophosphate produced by these reactions, thereby improving the efficiency of the reaction by inhibiting the detrimental pyrophosphorolysis reaction.” *Id.* A person having ordinary skill in the art is cited to have reasonable expectation of success because Tabor et al. teach that “inorganic pyrophosphatase was commercially available.” *Id.*

The explanations articulated in Paper No. 20081110, lead Applicants to the assumption that the rationale for obviousness corresponds to rationale (G) of the KSR obviousness examination guidelines namely that the Examiner has found some teaching, suggestion, or motivation in the Kwok et al. and Tabor et al. that would have led one of ordinary skill to

combine the Kwok et al. and Tabor et al. teachings to arrive at the claimed invention. The requirements for an obviousness rejection based on this rationale are listed on page 57534 of the Federal Register, Vol. 72, No. 195 and are reproduced below.

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Implicit in this rationale is a showing that Kwok et al. and Tabor et al. when combined produce the claimed invention. This is fully in line with historical precedent supported by the holding in *KSR*, that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The CAFC has further interpreted *KSR* as applied to the biological arts to require an explicit showing that the prior art would have suggested making the specific modifications necessary to achieve the claimed invention. This standard was affirmed in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, where the Federal Circuit reaffirmed the teaching, suggestion, and motivation test “flexibly applied” so as to require that any *prima facie* case of obviousness must be accompanied by an explicit showing where the relied on prior art provided the requisite teaching, suggestion, or motivation. 520 F.3d 1358, 1364-65 (Fed. Cir. 2008). Applicant submits that the prior art of record fails to provide, explicitly or inherently, any

teaching, suggestion, or motivation that would lead a person having ordinary skill in the art to the instantly claimed invention.

#### Substantive Distinctions between Prior Art Reference Combination and Claimed Invention

The teaching of Kwok et al. alone or in combination with Tabor et al. fails to teach or suggest numerous elements of the pending claims.

Regarding independent claims 1 and 26, and as previously made of record 4 August 2008, Applicants respectfully submit that neither Kwok et al. nor Tabor et al. teach or suggest incubating a product of a nucleic acid synthesis reaction amplified in the absence of an inorganic pyrophosphatase with an inorganic pyrophosphatase to yield a purified reaction product.

Paper No. 20081110 at page 9 states that Applicants' previous arguments were unpersuasive because: "The claims do not exclude the method resulting from the combined teachings of Kwok and Tabor, wherein the nucleic acid synthesis reaction product is produced and treated with the pyrophosphatase enzyme present in the nucleic acid synthesis reaction mixture to produce the purified reaction product." Claims 1 and 26 are currently amended to clarify that the product of the nucleic acid synthesis reaction is amplified in the absence of an inorganic pyrophosphatase, thus, excluding the method resulting from the combined teachings of Kwok and Tabor.

Tabor et al. teach adding an inorganic phosphatase to a PCR amplification reaction. In contrast, independent claims 1 and 26 recite that the amplifying is performed in the absence of inorganic pyrophosphatase. Simply because an inorganic pyrophosphatase may improve the efficiency of a PCR reaction does not teach or suggest to a person having ordinary skill in the art using an inorganic pyrophosphatase to treat a product of a nucleic acid synthesis reaction as

required by the subject claims because the efficiency improvements in Tabor et al. are no longer required after the product is formed.

Secondly, the requirements under rational (G) require a showing of a reasonable expectation of success. This showing must be both rational and more than a mere conclusory statement. “Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some rational underpinning to support the legal conclusion.” *KSR Int’l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007). The articulated underpinning for a reasonable expectation of success in Paper No. 20081110 at page 6 is that “Tabor taught that inorganic pyrophosphatase was commercially available.” The commercial availability of a reagent does not provide motivation for its use in an inventive method. “As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 127 S. Ct. at 1741 (citing *United States v. Adams*, 383 U.S. 39 (1966)). Similarly, a reasonable expectation of success is not provided simply because a reagent is available on the market place. As such, it is submitted that no reasonable expectation of success is provided or articulated from the cited teaching of Tabor et al.

In light of the foregoing amendments and remarks, Applicant submits that independent claims 1 and 26 are nonobvious over the prior art of record in that the combination of Kwok et al. and Tabor et al. fails to teach or suggest all elements of the pending claims, or provide motivation or a reasonable expectation of success for all elements of the pending claims. Similarly, dependent claims 2-7, 9, 10, 13-16, 21, and 27-30 are submitted to be patentable and nonobvious as dependent from a nonobvious base claim. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

In addition, Paper No. 20081110 at page 10 further asserts that one of ordinary skill and the art would be motivated to inactivate an inorganic pyrophosphatase from Tabor's teaching inactivating enzymes used to treat a nucleic acid synthesis product such that claims 6 and 30 are obvious thereover. The basis of this assertion is that one of ordinary skill in the art would recognize that the activity of the inorganic pyrophosphatase, like the activities of exonuclease I and shrimp alkaline phosphatase, is no longer necessary. *Id.* Applicant respectfully submits that a person of ordinary skill in the art would find motivation for the opposite action from the asserted teaching of Tabor. If the presence of an inorganic pyrophosphatase increases the efficiency of a nucleic acid in a synthesis reaction, such a person would not be motivated to inactivate the inorganic pyrophosphatase as this would decrease the efficiency of the subsequent incorporation reaction. Thus, one of the ordinary skill in the art would be motivated from the asserted teaching of Tabor et al. to include an inorganic pyrophosphatase that has not been inactivated in a subsequent primer extension step. As such, claims 6 and 30 have independent bases of patentability.

Finally, Kwok et al. and Tabor et al. fail to teach or suggest performing all the claimed steps in a single reaction chamber as required by subject claim 21. As such, it is submitted that claim 21 possesses an independent basis of patentability.

Additional bases of patentability exist, and Applicant reserves the right to make these of record in the course of prosecution as necessary.

In light of the foregoing amendments and remarks, withdrawal of the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. in view of Tabor et al. is respectfully requested.

**Remarks directed to the rejection of claims 18 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2).**

Withdrawal of the rejection of claims 18 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2) is respectfully requested because no teaching of Jack et al. corrects the aforementioned deficiencies in Kwok et al. or Tabor et al. to teach or suggest all elements of independent claim 1 from which claims 18 and 23 depend. As such, the cited prior art combination of Kwok et al., Tabor et al, and Jack et al. fails to teach or suggest all elements of the claimed invention as required for any finding of obviousness.

Additional bases of patentability exist, and Applicant reserves the right to make these of record in the course of prosecution as necessary.

In light of the forgoing remarks, withdrawal of the rejection of claims 18 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2) is respectfully requested.



### **SUMMARY**

Claims 1-7, 9, 10, 13-16, 18, 21, 23 and 26-30 are currently pending in the application. All pending claims are submitted to be in allowable form and directed to patentable subject matter. Reconsideration and withdrawal of the rejections is, thus, respectfully requested.

Should the Examiner have any questions, Applicant's attorney may be reached at the telephone number given below.

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Respectfully submitted,

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